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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	12

DATE MAILED: 02/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/888,358	Applicant(s) ADAMS ET AL.	
	Examiner Sally A Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32 and 35-43* is/are pending in the application.

4a) Of the above claim(s) *1-31,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 & 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group X in Paper No. 11 is acknowledged. Applicant's arguments filed 12/26/02 have been fully considered but they are not persuasive. Applicant's election with traverse of Group X, claims 32 and new claims 35-43 in paper No. 11 is acknowledged. The traversal is on the ground(s) that the office has mischaracterized the relationship between the products of Groups I, II, III, IV, VIII and IX. The examiner maintains that each group is characterized by its distinct biomolecule, nucleic acid. protein, antibody etc, each being distinct as their composition is drastically different, ie nucleic acids are composed of nucleotides joined by phosphodiester linkages, while proteins are composed of sequential amino acids joined by peptide bonds. Traversal was also on the grounds that the method groups V, VI, VII, X and XI were separated on only asserted characteristics. Applicant should note however, that method steps directed to, for example modulating activity, treating a disorder, and screening for a mutation all require very different method steps and reagents because of their distinct compositions and varied applications. Lastly Applicant traversed on the grounds that the no examples or support were provided for the separation of Groups VIII and IX. Examiner reaffirms that the groups are properly separated as their inclusive products are comprised by different nucleic acid sequences and as a result, create distinct transgenic non-human animals. The examiner maintains the restriction requirement made previously, as each group is correctly separated as unrelated or patentably distinct entities.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of U.S. Provisional Application 60/213,307 filed June 22, 2000 is granted.

35 U.S.C. 101/112 Utility Rejections

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

> "Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

> "Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be

specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of

> one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at 2107 - 2107.02.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 32 and 35-43 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility.

The claimed nucleic acid methods are not supported by a specific asserted utility because the disclosed method of screening is not specific and is generally applicable to any nucleic acid. The specification teaches that using differential display mRNA expression analysis, a previously-uncharacterized gene was found to be up regulated 2-fold in brown adipose tissue (BAT) of mice exposed to cold (4°C) for 48 hr. Contig and homology analysis revealed that the gene represents the murine ortholog to a public database sequence encoding a putative human protein (CGI-69). Isolation of CGI-69 cDNA from human liver revealed variants of CGI-69, including a previously undescribed nucleic acid encoding a "long version" of CGI-69. The specification states that the screening for these mutations will aid in the discovery of genes whose sequences "lead to biological changes that predispose to metabolic disease, or are in fact predictive of the progression of disease"(specification, page 2). The specification adds that "while not being bound by any particular theory, CGI-69 may be involved in cellular thermogenic uncoupling and, therefore, may be utilized to diagnose and treat specific perturbations in

metabolic pathways underlying obesity and other metabolic disorders"(Pg. 6). The specification on page 15 teaches that "the full or partial length native sequence CGI-69 may be used to pull out similar homologous sequences such as: full length or fragments of CGI-69 cDNA from a cDNA library from any species, from cells or tissues, variants within a species, and homologues and variants from other species. All of the aforementioned are non-specific uses that are applicable to nucleic acid(s) in general and not particular or specific to the nucleic acid(s) required to perform the claimed methods.

Further, the claimed methods are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a nucleic acid may be utilized to obtain a protein. The protein could then be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving claimed nucleic acid have asserted or identified specific and substantial utilities. The research contemplated by applicants to map genomes, physical mapping, positional cloning, and in functional genomics does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. The claimed methods require the use of a nucleic acid, CGI-69, for which a specific and substantial utility has not been established. Additionally, the specification has not established a specific and substantial utility for any mutations in a CGI-69 nucleic acid. Accordingly, methods of searching for new mutations in the CGI-69 nucleic acids constitute a research project. While one could perform methods that search for alterations in the CGI-69 gene, then assay these alterations to try to determine whether the alterations are associated with the occurrence of metabolic disease, such a use is not

specific or substantial. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid method such that another non-asserted utility would be well established for the claimed methods.

2. Claims 32 and 35-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Furthermore, it is noted that Claims 32 and 35-43 are broadly drawn to methods of screening for a mutation in CGI-69 comprising comparing any nucleic acid sequence to the sequence of SEQ ID NOS: 1 or 2. As discussed above in the utility rejection, the specification does not clearly set forth the location of the mutations within the sequence of CGI-69 nor does it clearly set forth the functional consequences of any mutation in CGI-69. Furthermore, the specification teaches the screening for a mutation in CGI-69 by comparison to SEQ ID NOS: 1 and 2. The specification teaches SEQ ID NO:1 to be a splice variant, and as a result a longer version of SEQ ID NO:2. However the specification also teaches that both sequences are to be used as reference sequences. It is not clear in what way the splice variant was discovered, if it was itself, the result of a mutation that caused a frameshift and the resulting "longer version" of CGI-69. The specification does not specify any examples of said putative "mutation's" ability to predict susceptibility to any of the metabolic diseases. The specification further excludes any teachings of the biochemical effect of the mutation on SEQ ID NOS: 1 and 2 and the

way in which it confers the putative, resulting, diseased phenotype or detectable characteristic. The specification does not teach all of the possible structures encompassed by "mutations in CGI-69" nor does it provide an explanation as to why and where each of the different mutations when compared to SEQ ID NOS: 1 or 2 will provide any telling data. It is not clear if the comparison to SEQ ID NO:1(CGI-69 splice variant, itself, containing a possible mutation) will yield different results than the same comparison to SEQ ID NO:2(CGI-69). For example, the specification does not teach if the variant is the result of a deletion, same sense, missense, or nonsense mutation or if it results in a transition, transversion, etc. The specification further omits teachings of how each variant's structure is responsible for the resulting phenotype or lack thereof. Therefore, the specification does not at all, enable how to use this method of screening for a mutation in CGI-69 comprising comparing a nucleic acid sequence to the sequence of SEQ ID NOS: 1 or 2. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added).

The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. The prior art is silent with regard to mutations in CGI-69. However, there is a large body of knowledge in the prior art related to uncoupling protein(UCPs) homologs in general, and their tenuous relationship to metabolic diseases or disease states. The art is highly unpredictable with regard to the functionality of a homolog of a gene described in rodents and mice brown adipose tissue(BAT) as an UCP. Adams teaches the unpredictability of extrapolating this data from other species such as rodent or mouse. The reference teaches

that, "UCP2" is an interesting candidate for involvement with thermogenesis. However, expression data yield conflicting evidence for the role of UCP2 in situ"(Adams Pg.712). The reference teaches that while UCP2 expression is induced in a leptin deficient mouse(ob/ob) and leptin administration to these ob/ob mice was able to normalize liver proton leak, "but unfortunately leptin-induced changes in hepatocyte UCP2 expression were not present"(Adams, 712). The reference teaches that a homolog to an originally isolated, over-expressed UCP, does not always retain its function in a different system. The art further teaches that another homolog, to UCP2, has produced "numerous data which raise the question whether UCP2 acts as an uncoupler in situ. Lastly, Adams teaches that with respect to another UCP, that "studies correlating UCP3 expression with metabolic status do not yield compelling evidence to confirm an important contribution of this homolog's activity toward driving metabolic rate in vivo". The reference concluded by admitting that, most analyses of putative UCP homologs rely on indirect indices of function, and challenges remain to optimize such assessments further"(Adams 713). Thus, even for the extrapolation of a homolog or ortholog's function from one system to another, in addition to the detection of mutations, it is highly unpredictable as to whether a particular sequence will be disease associated. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily

anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different "wild-type" or reference sequences, it remains highly unpredictable as to the biological significance of any mutation within CGI-69 as compared to these reference sequences. Thus, the use of the claimed method of screening for a mutation in CGI-69 as compared with SEQ ID NOS: 1 and 2, or the diagnosis or prognosis of disease via detection of these mutations, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected method of screening and some phenotypic trait. Even if the prophesized mutations are in some way associated with some metabolic disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the mutation is associated. That is, it is unpredictable as to whether the presence of a particular allele, splice variant, truncation, etc the mutation would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to screen for a mutation in the putative human protein, CGI-69 that is somehow related a metabolic disease.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards the mutations in CGI-69, applicant speculates that these mutations will aid in the discovery of genes whose sequences "lead to biological changes that predispose to metabolic

disease, or are in fact predictive of the progression of disease"(specification, page 2). However, since the effects of any given mutation on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed screening method for nucleic acids. That is, the specification does not provide any guidance as to how the mutation as compared to the splice variant of SEQ ID NO:1 and the other version SEQ ID NO: 2 would be associated with any method of screening. The specification does not discuss whether this particular mutation will increase the likelihood of a positive or negative response to any drug. The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed method or mutations found in the screen as markers for any disease in particular, or for disease in general.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the mutation of CGI-69 and some physiological or disease state. Indeed, even to use the method of claim 32 to detect disease associated with a mutation in a sample nucleic acid, one would need to know that the mutation in CGI-69, was in some way associated with the underlying biochemical process leading to a specific disease. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method of

screening for a mutation would be useful in disease detection, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between any mutation and any disease or condition.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, with respect to claim 32 undue experimentation is required in order to determine how to use the screening method of claim 32. With respect to the present invention, one cannot readily anticipate the application to the screening of any mutation in any CGI-69 as compared to SEQ ID NOS: 1 or 2 as presently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 32 and 35-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 32 and 35-43 are indefinite and vague because the claims do not recite the basic steps of the claimed method in a positive, active fashion (see Ex parte Erlich 3 USPQ2d, 1011 (BPAI 1986). "comparing" is a vague term and does not clearly set forth the method steps required to identify a mutation in CGI-69 molecule. The term includes

performing a mental step and is not considered to be an active process step. The claims lack any positive process steps. For example, in the instant case, the Applicant could amend Claim 32 to "A method of screening for a mutation in CGI-69 comprising hybridizing...". Applicant should note that in claims 38 and 39, "by polymerase chain reaction" and "by nucleic acid hybridization" respectively, are not active process steps and also require amendment.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris
2/5/2003

CARLA J. MYERS
PRIMARY EXAMINER